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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,799	05/04/2005	Graeme Semple	22578-003US1 032.US2.PCT	6923

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EXAMINER	
CHUNG, SUSANNAH LEE	
ART UNIT	**PAPER NUMBER**
1626	
MAIL DATE	**DELIVERY MODE**
06/27/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,799	SEMPLE ET AL.	
	Examiner	Art Unit	
	SUSANNAH CHUNG	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,20,21 and 26-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,20,21 and 26-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/8/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-14, 20, 21, and 26-28 are pending in the instant application.

Priority

This application is a 371 of PCT/US03/35427, filed 11/04/2003, which claims benefit of 60/423,819, filed 11/05/2002.

Information Disclosure Statement

The information disclosure statement (IDS), filed on 1/8/08 has been considered. Please refer to Applicant's copy of the 1449 submitted herewith.

Response to Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 5/6/08 is acknowledged.

The traversal is on the following grounds that the basis of the restriction was not for a 371 application, but rather a US application and thus rejoinder is requested. **The restriction requirement mailed on 11/6/2007 is withdrawn** and all the claims are examined for patentability.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-21 and 26-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims, for the reasons describe below.

As stated in MPEP 2164.01(a), "there are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

The factors to be considered when determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, were described in In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) as:

1. the nature of the invention;
2. the breadth of the claims;
3. the state of the prior art;
4. the relative skill of those in the art;
5. the predictability or unpredictability of the art;
6. the amount of direction or guidance presented [by the inventor];
7. the presence or absence of working examples; and
8. the quantity of experimentation necessary [to make and/or use the invention].

The eight Wands factors are applied to Claims 20-21 and 26-27 of the present invention below:

(1) The Nature of the Invention

Claims 20-21 and 26-27 are directed to methods of treating a metabolic-related disorder comprising administering to an individual in need of such treatment a therapeutically effective amount of a pharmaceutical composition of claim 13 or of a compound of claim 1.

(2) The Breadth of the claims

Claims 20-21 and 26-27 will be give its broadest reasonable interpretation. The applicable rule for interpreting the claims is that "each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." See MPEP 2163(II)(1), citing In re Morris, 127 F.3d 1048, 1053-1054; 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). In view of this rule, Claims 20 and 26, which do not specify the many possible metabolic-related disorders will be interpreted to encompass all metabolic-related disorders. Claims 21 and 27, which specify the disorders dyslipidemia, atherosclerosis, coronary hear disease, insulin resistance, and type 2 diabetes will be examined to see if there is support in the specification and prior art for these disorders, regardless of whether it is a primary or secondary method of use.

(3) The state of the prior art

The state of the art at the time of this application was that certain benzotriazole compounds exhibit useful pharmaceutical properties as PPAR agonists and could be used to treat dyslipidemic type 2 diabetes or dyslipidemia without diabetes. (See Sparatore, et al., Chem & Biodiver., Vol. 3, 2006, 385-395, especially page 390, approx. lines 10-15.)

The use of benzotriazole compounds as selective agonists of the Human Orphan G-Protein-Coupled Receptor GPR109b is also known. Studies have shown that the benzotriazole derivatives can be used to treat dyslipidemia and atherosclerosis. (See Semple, et al., J. Med. Chem. 2006, 49, 1227-1230, especially page 1229, column 2, approx. lines 28-31.)

It should be noted that the instant application is not directed to PPAR or GPR109b, but rather hRUP38. The, current state of the art is that benzotriazole compounds are useful in treating some diseases wherein the mechanism of action is PPAR or GPR109b, but not hRUP38.

Therefore, guidance is sought from the instant specification as to whether these compounds are enabled as hRUP38 agonists and could treat specific disorders.

(4) The relative skill of those in the art

The level of skill in the art (pharmaceutical chemists, physicians) would be high.

(5) The predictability or unpredictability of the art

It is noted that the pharmaceutical art generally is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement varies inversely with the degree of unpredictability in the factors involved. In re Fisher, 427 F.2d 833, 839. Therefore, the more unpredictable an area, the more specific enablement is needed in order to satisfy the statute. Added to the unpredictability of the art itself is the question whether the compound of the present invention could be reliably and predictably extrapolated to patients with all the metabolic-related disorders claimed. There is no absolute predictability, even in view of the high level of skill in the art.

(6) The amount of direction or guidance presented (by the inventor)

The specification in the present invention discloses that the instantly claimed compounds can be used to treat metabolic-related disorders. The mechanism of action used by the instantly claimed benzotriazole compounds is that they are agonists of hRUP38. Applicants provide some data, but do not show with any level of specificity how the instantly claimed compounds are agonists of hRUP38 or how they treat specific metabolic-related disorders. Therefore, there is insufficient guidance in the specification for the role the instantly claimed compounds play as agonists of hRUP38 or the role the instantly claimed compounds play in treating all metabolic

related disorders, including, but not limited to dyslipidemia, atherosclerosis, coronary hear disease, insulin resistance, and type 2 diabetes.

(7) The presence or absence of working examples

The specification discloses the general role of the instantly claimed benzotriazole compounds in an in vivo animal model on page 64 of the specification, but there is very little data provided to show how the instantly claimed compounds are hRUP38 agonists or how the instantly claimed compounds act to treat a disorder. In particular, there are no working examples of how a particular compound is used to treat a particular disorder or of the general mechanism of action used as an hRUP38 agaonist. The data provided lists some dosage requirements, but never mentions hRUP38 or any specific disorder.

In addition, Applicants provide a receptor binding assay in Example 8 on pages 65-67 of the specification, but the assay does not provide specific data showing the binding capability of any of the instantly claimed compounds. It is assumed that the binding assay was provided to show that the instantly claimed compounds bind to RUP38, but specific data is required to show the level of binding and which compounds were used for the assay.

(8) The quantity of experimentation necessary (to make and/or use the invention)

Given the absence of direction or guidance (or working examples) in the specification for the role of the instantly compounds as hRUP38 agonists to treat metabolic disorders, it would cause a skilled artisan an undue amount of experimentation to practice this invention to determine which patients with which diseases would benefit from which of the many claimed compounds within the scope of the invention with a reasonable expectation of success. Therefore, the claims are not enabled.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2 12, 13 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds and compositions of formula (I), does not reasonably provide enablement for solvates or hydrates of those compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The claims recite specific compounds of structural formula (I), the solvates and hydrates of said compounds. However, the specification fails to teach the preparation of solvates or hydrates. Therefore, the specification is not adequately enabled for solvates and hydrates.

Identifying a solvate requires knowledge of properties of the solvents and solutes of the instant compounds and nothing short of extensive testing (none identified) would be needed to determine if additional derivatives exist thus, such a scope as literally claimed herein is not enabled.

The examples presented all fail to produce a solvate or hydrate. These cannot be simply willed into existence. As was stated in Morton International Inc. v. Cardinal Chemical Co., 28 USPQ 2d 1190, "the specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However…there is no evidence that such compounds exist…the examples of the `881 patent do not produce the postulated compounds…there is…no evidence that such compounds even exist." The same circumstance

appears to be true here. There is no evidence that solvates or hydrates of the instantly claimed compounds exist. If they did, they would have been formed. Hence, applications must show that solvates and hydrates can be made, or limit the claims accordingly by deleting the terms solvates and hydrates.

It is not the norm that one can predict with any accuracy a particular solvate form of an active compound will be more soluble, more easily handled in formulations or more bioavailable without actual testing in vivo. The specification provides no guidance as to what types are suitable for the instantly claimed compounds.

The factors to be considered when determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, were described in In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) as:

1. the nature of the invention;
2. the breadth of the claims;
3. the state of the prior art;
4. the relative skill of those in the art;
5. the predictability or unpredictability of the art;
6. the amount of direction or guidance presented (by the inventor);
7. the presence or absence of working examples; and
8. the quantity of experimentation necessary (to make and/or use the invention).

The eight Wands factors are applied to Claims 1, 2, 12, 13 and 28 of the present invention below:

(1) The Nature of the Invention

The nature of the invention is the compounds of formula (I). In addition to the compounds, the salts, solvates and hydrates are also claimed.

(2) The Breadth of the claims

The breadth of the claims encompass salts, solvates and hydrates of the compounds of formula (I). The applicable rule for interpreting the claims is that "each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." See MPEP 2163(II)(1), citing In re Morris, 127 F.3d 1048, 1053-1054; 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). In view of this rule, all of the potential salts, solvates and hydrates that could be formed will be interpreted to be encompassed by the instant claims.

(3) The state of the prior art

It was known in the art at the time of this application that compounds can exist in salt, solvate and hydrate form.

(4) The relative skill of those in the art

The level of skill in the art (pharmaceutical chemists, physicians) would be high.

(5) The predictability or unpredictability of the art

The predictability of the art with regard to salts is known, but the preparation of solvates and hydrates are compound specific. In addition, the extremely large scope of the potential solvates and hydrates that could be produced using the compound of formula (I) renders the prior art unpredictable for making or using products as claimed on such a grand scale.

(6) The amount of direction or guidance presented (by the inventor)

There is no guidance in the specification drawn to the solvates and hydrates of the instantly claimed compounds of formula (I). In addition, the specification provides no guidance as to what type(s) of solvates are suitable for the instantly claimed compounds.

(7) The presence or absence of working examples

The specification has no working examples of solvates or hydrates of the instantly claimed compounds.

(8) The quantity of experimentation necessary (to make and/or use the invention)

The quantity of experimentation is undue given the absence of direction or guidance (or working examples) in the specification for the extremely large number of solvates and hydrates that could be encompassed by the claims. Identifying a solvate requires knowledge of the properties of the solvents and solutes and their reactions and/or transformation, nothing short of extensive testing (none identified) would be needed to determine if additional derivatives exist and thus, such as scope as literally claimed herein is non-enabled.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The agents

α-glucosidase inhibitor, aldose reductase inhibitor, biguanide, HMG-CoA reductase inhibitor, squalene synthesis inhibitor, fibrate, LDL catabolism enhancer, angiotensin converting enzyme inhibitor, insulin secretion enhancer and thiazolidinedione.

of the composition are not defined in the specification so as to know the structures of the compositions that are included and/or excluded by the term. Therefore, the specification lacks adequate support for Claim 14.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the claim is indefinite because the claim states that an agent is further included in the composition. The agents listed are

α-glucosidase inhibitor, aldose reductase inhibitor, biguanide, HMG-CoA reductase inhibitor, squalene synthesis inhibitor, fibrate, LDL catabolism enhancer, angiotensin converting enzyme inhibitor, insulin secretion enhancer and thiazolidinedione.

The metes and bounds of the claim are unclear. It is not possible that all current and potential α-glucosidase inhibitors can be agents for the instantly claimed composition. (See 25 USC 112, 1st rejection.) Further explanation of the metes and bounds of the claim are required. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

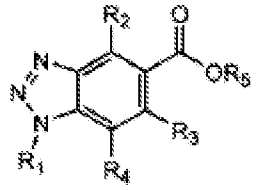
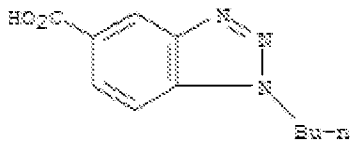
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 5, 6, 7, 8, 12, 13, and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Raeymaekers, et al (U.S. Pat. No. 4,943,574).

Applicants claims of substituted benzotriazole carboxylic acid compounds relate to Formula (I) of claim 1,  . Raeymaekers discloses the species  , 1-butyl-1H-benzotriazole-5-carboxylic acid, CAS RN 120321-66-6, found in Example 2, Column 21, approx. lines 57-58, which anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

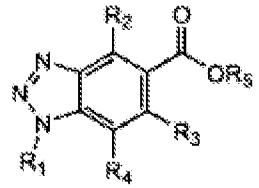
The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-14 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raeymaekers, et al (U.S. Pat. No. 4,943,574).

Applicants instant elected invention teaches benzotriazole compounds of formula,



, depicted in claim 1, yielding 1-butyl-1H-benzotriazole-5-carboxylic acid as one of the species, wherein the compounds are used pharmaceutically to treat metabolic disorders.

Determination of the scope and content of the prior art (MPEP § 2141.01)

Raeymaekers teaches the species 1-butyl-1H-benzotriazole-5-carboxylic acid (found in Example 2, Column 21, approx. lines 57-58) and 1-methyl-1H-benzotriazole-7-carboxaldehyde (found in Example 3, Column 22, approx. lines 48-49), wherein the compounds are used pharmaceutically to treat disorders ranging from estrogen to thromboxane synthetase diseases.

Ascertainment of the difference between the prior art and the claims (MPEP § 2141.02)

The difference between the prior art of Raeymaekers and the instant claims is that the instant claims are directed to a genus, while the prior art is directed to a species.

Finding of prima facie obviousness – rationale and motivation (MPEP § 2142-2413)

In the absence of showing unobvious results, it would have been obvious to one of ordinary skill in the art at the time of the invention when faced with Raeymaekers to make a genus from a prior art species. A species will anticipate or render obvious a claim to a genus.

See MPEP 2131.02. "A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus." The species in that case will anticipate the genus. In re Slayter, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); In re Gosteli, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989) (Gosteli claimed a genus of 21 specific chemical species of bicyclic thia-aza compounds in Markush claims. The prior art reference applied against the claims disclosed two of the chemical species. The parties agreed that the prior art species would anticipate the claims unless applicant was entitled to his foreign priority date.).

In addition, the prior art teaches the process of making a species claimed in the instant application. One of ordinary skill in the art would be able optimize the reaction conditions to include other more generic compounds based on the teachings of Raeymaekers.

Therefore, in view of the prior art teaching the species and the instant claims being directed to a generic claim of the species, the claims are rendered obvious by the prior art compound and the process of making the compound.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susannah Chung whose telephone number is (571) 272-6098. The examiner can normally be reached on M-F, 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/REI-TSANG SHIAO /
Primary Examiner, Art Unit 1626

Susannah Chung, June 19, 2008